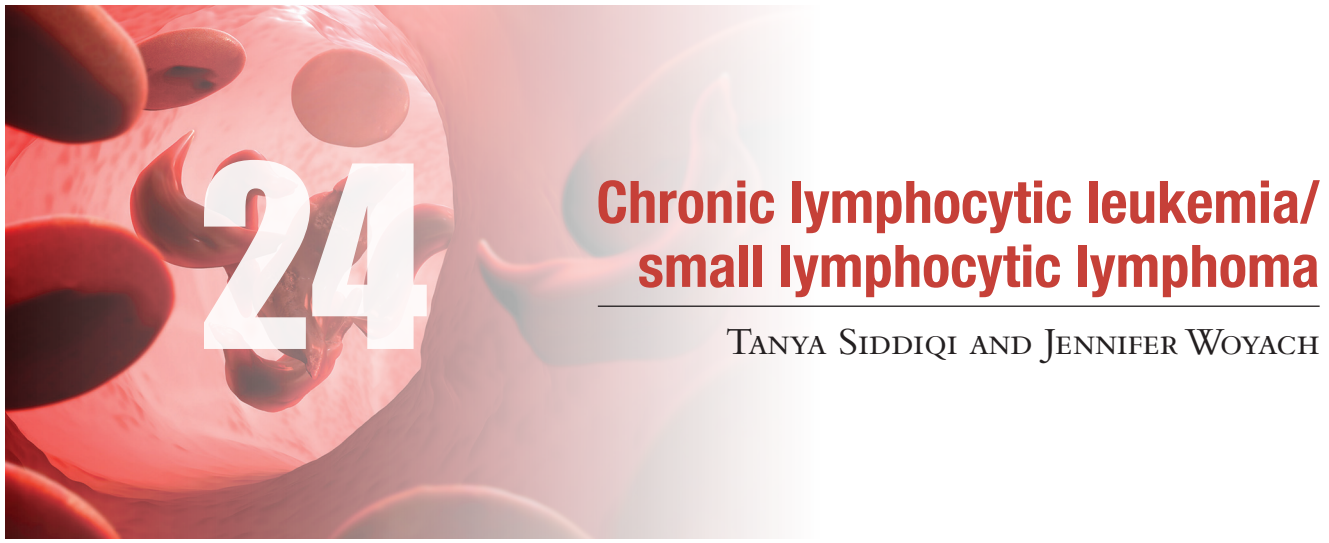

24 Chronic lymphocytic leukemia/ small lymphocytic lymphoma

Tanya Siddiqi and Jennifer Woyach

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The online version of this chapter contains an educational multimedia component on chronic lymphocytic leukemia.

Epidemiology

Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) is the most prevalent lymphoid malignancy in North America and Europe and is less common among people of African or Asian origin. It accounts for 25% to 30% of leukemia cases in the United States, with an estimated incidence of approximately 21,250 new diagnoses in 2021. The estimated prevalence of CLL in the United States is 120,000 to 140,000 persons. The median age at diagnosis is 72 years, with an incidence rate in men twice that of women.

Biology

Cell of origin

CLL is an indolent malignancy of mature B cells. The cell of origin for CLL is not fully defined. CLL cells from patients with somatically hypermutated and unmutated immunoglobulin heavy-chain variable region (IGHV) (see "Pathophysiology") have a similar gene-expression profile, which suggests a common cell of origin for CLL. Functional, immunophenotypic, and gene-expression data suggest that CLL is most closely related to the $CD5^+$ B-1 B-cell subpopulation. In human adults, B-1 cells constitutively produce polyreactive-antimicrobial (natural) antibodies that are an important component of innate immunity.

Etiology

The cause of CLL remains unknown. There is considerable evidence to suggest a genetic predisposition to the disease. The risk of CLL in diverse populations is highly variable, with the highest risk in populations with northern European genetic heritage and a considerably lower incidence in populations of East Asian genetic heritage, irrespective of where they live. In addition, for the 5% to 10% of patients with familial CLL, their first-degree relatives have a significantly increased risk (~8.5-fold) of developing CLL or another B-cell malignancy. However, the clinical course of familial CLL in individuals with the disease is not determined by familial status, which suggests that the familial component pertains only to the risk of acquiring the disease. Genome-wide genetic studies in familial and sporadic CLL cohorts have implicated over 40 germ line genetic polymorphisms. Therefore, it is unlikely that CLL predisposition is related to

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Off-label drug use: CAR-T cells.

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a single genetic defect. Extensive studies have established that there are limited environmental risk factors for CLL.

Pre-CLL conditions

Aging is associated with major changes in both innate and adaptive immunity, including decreased antibody repertoire and increased frequency of oligoclonal B-cell populations. When people 60 years of age and older with normal complete blood counts are screened with high-sensitivity flow cytometry, >5% have small circulating monoclonal B-cell populations that are of unknown clinical importance. This condition is termed *monoclonal B-cell lymphocytosis* (MBL). By definition, MBL is not associated with organomegaly, lymphadenopathy, or abnormal blood count results. The high prevalence of this condition suggests that the development of CLL is a stepwise process, affecting only a small percentage of patients with a preexisting monoclonal population of B cells. The presence of <50 clonal B lymphocytes/μL is termed low-count MBL while the presence of >2000 (but <5000) clonal B lymphocytes/μL is termed high-count MBL. High-count MBL is associated with a 15% risk of developing CLL over a median of 6.7 years and is associated with risks of bacterial infections and secondary malignancies similar to those of CLL.

Pathophysiology

CLL is a disease typically characterized by peripheral blood lymphocytosis. When lymph node involvement occurs, it is characterized by the progressive accumulation of monoclonal B cells that preferentially grow in the proliferation centers (pseudofollicles) of lymph nodes with an overall tumor-cell proliferation rate of 0.1% to 1% per day and prolonged overall cell survival (~3-6 months) because of defective apoptosis. An important driver of CLL survival and growth is B-cell receptor (BCR) signaling, and multiple mechanisms of sustained activation of the BCR in CLL have been described. Antigen-binding specificity of BCR is determined by the composition of the variable regions of the immunoglobulin molecule. Some CLL clones share BCRs with similar amino acid sequences (stereotyped BCRs) and this can be seen in ~30% CLL cases, primarily those with unmutated IGHV. These stereotyped BCRs have highly homologous heavy-chain complementarity-determining region 3s (CDR3s), often encoded by identical IGHV, IGHD, and *IGHJ* segments. Many stereotyped BCRs also use the same IGKV or IGLV, such that the κ CDR3s and λ CDR3s are also very similar in protein structure. Studies have shown that CLL idiotypic antibodies frequently react to autoantigens, including antigenic targets on apoptotic cells, tend to be polyreactive and, in some cases, can even be activated by self-epitopes. These findings provide important insights into the biology of CLL and have also identified the BCR and its signaling pathway as therapeutic targets (see video in online edition).

Antigen-responsive B lymphocytes in the germinal center can be induced to undergo antigen-driven somatic hypermutation of the immunoglobulin genes, which alters epitope affinity for antigen. Somatic hypermutation of the variable region of IGHV is defined as ≥2% sequence difference from germ line and occurs in >50% of patients with CLL. CLL patients with these "mutated" IGHVs generally have a less aggressive disease course and better overall survival (OS) rate. In contrast, patients with CLL cells that have not undergone somatic hypermutation of IGHV (so-called unmutated CLL) generally have a more aggressive disease and poorer outcome; although, this difference in prognosis may no longer exist with the new oral targeted drugs. While patients with unmutated CLL have cells that are responsive to BCR cross-linking in vitro, patients with mutated IGHV tend to have CLL cells that are anergic. However, the relationship among IGHV mutation status, BCR activation, and CLL disease biology is not yet fully understood.

CLL cells have apoptotic defects that contribute to increased survival in the stromal microenvironment of the lymphoid tissues and bone marrow. Important components of apoptosis resistance include increased dependence on the antiapoptotic molecules BCL2 and MCL1. The molecular mechanisms of these defects are not fully understood. However, 13q14 deletion, the most common defect detected in CLL by interphase fluorescent in situ hybridization (FISH), results in the deletion of genes coding for the inhibitory microRNAs (miRs) *miR15* and *miR16* that downregulate expression of the *BCL2* gene. The mechanism by which BCL2 expression is upregulated in CLL patients without 13q14 deletion may be related to miRs.

Defects in the DNA damage-repair pathway in CLL cells are associated with more aggressive disease, cause resistance to DNA-damaging chemotherapies, and increase the risk of disease transformation. These defects are an important but rare event in CLL patients at diagnosis (<10%). Defects increase in frequency with disease progression and occur in ~50% of patients refractory to therapies containing DNA-damaging chemotherapy. *TP53* defects disrupting p53 protein function occur either because of loss of 1 allele of *TP53* by 17p13 deletion and a dysfunctional mutation in the remaining *TP53* allele, biallelic dysfunctional mutations, or a single dominant-negative mutation. Disruption of ATM function can also result in a defective DNA damage-repair pathway in CLL cells. One allele of ATM is lost in the 11q22.3 deletion, and complete loss of function of ATM in these cells can occur because of disruptive mutations in the remaining allele.

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Loss of ATM function can also occur because of biallelic disruptive ATM mutations.

The pathophysiological effects of CLL cells are complex and not fully understood. Accumulation of CLL cells in the lymph nodes, spleen, and liver cause enlargement and disruption of function of these organs. Bone marrow infiltration and the effects of CLL cells on myelopoiesis and the bone marrow microenvironment can decrease hematopoiesis, which results in cytopenias. CLL cells have an early detrimental effect on normal immune function. The detrimental effect results in impaired immunological response to infection, defective immunological self-recognition, and possibly defective immune surveillance for other malignancies. The mechanism of the constitutional effects of progressive CLL, including weight loss, drenching night sweats, fevers, and fatigue, are not fully understood but could be the result of dysregulated cytokine production.

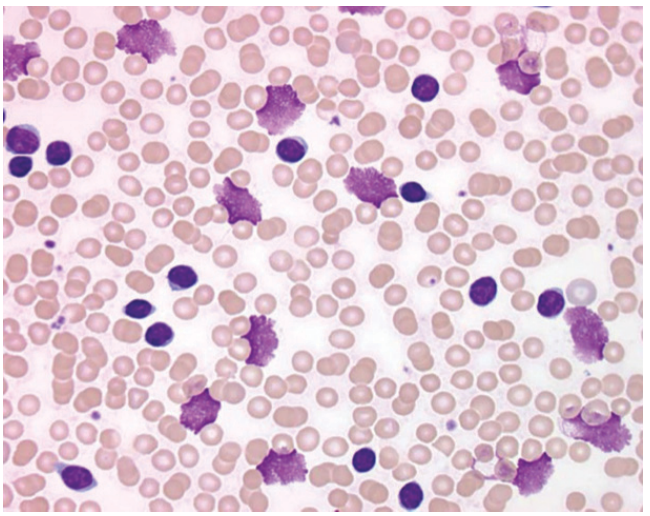

Figure 24-1 A peripheral blood smear of a patient with CLL (Giemsa stain; magnification ×400) shows small lymphocytes and numerous smudge cells.

KEY POINTS

- CLL is the most prevalent lymphoid malignancy in North America. The incidence of CLL increases with age.
- Risk of CLL is higher in populations of northern European heritage, and CLL is relatively uncommon in Asia.
- CLL is a familial disease in <10% of patients. Familial CLL does not increase the risk of a more aggressive disease course.
- Monoclonal B-cell lymphocytosis (MBL) is an established pre-CLL condition.

Diagnosis and clinical evaluation

Presentation

CLL, including the SLL variant, is usually diagnosed on evaluation of an incidental finding of asymptomatic leukocytosis/lymphocytosis or lymphadenopathy/splenomegaly. Only ~20% of patients have symptomatic disease at diagnosis. CLL can present with symptomatic anemia, bleeding owing to thrombocytopenia, symptomatic adenopathy or splenomegaly (abdominal distention or early satiety), or constitutional symptoms. Constitutional symptoms include profound fatigue, drenching night sweats, fevers, and involuntary weight loss.

In the contemporary era, when patients are diagnosed earlier than in historical series, physical examination observations are often normal at diagnosis. Possible physical findings include firm, rubbery nontender lymphadenopathy, which is frequently symmetrical, and palpable liver or spleen enlargement.

Diagnosis

Peripheral blood lymphocyte morphology

CLL cells have an appearance similar to normal small lymphocytes. CLL cells have increased cell-membrane fragility and tend to break during the process of making a blood smear, which gives rise to smudge cells that are characteristic, but not pathognomonic, of CLL (Figure 24-1). A subset of circulating CLL cells can also have prolymphocytic morphology. Higher percentages of prolymphocytes in the peripheral blood (>55%) of patients with immunophenotypically diagnosed CLL have previously been considered indicative of transformation to "secondary" B-cell prolymphocytic leukemia (PLL). However, this finding could indicate clonal evolution of CLL with a *MYC* translocation or other adverse event rather than transformation to a distinct second disease. The latter indication would be quite rare.

Peripheral blood flow cytometry

The diagnosis of CLL can be made by immunophenotypic characterization of peripheral blood lymphocytes by flow cytometry. B-cell clonality is determined by demonstrating light-chain restriction in the B ($CD19^+$) lymphocytes. CLL cells characteristically have dim CD20 and dim light-chain expression, and they coexpress CD5 and CD23. CD79b is a component of the BCR, and expression is usually dim or absent in CLL. Low CD20 expression can be confirmed by negative study results with the low-affinity CD20-binding antibody FMC7. If the monoclonal B cells do not have the typical CLL immunophenotype (monoclonal B cells that are CD20 dim,

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Table 24-1 Chronic B-cell lymphoproliferative disorders: immunophenotype

Disease	sIg	CD20	CD5	CD23	CD10	CD103
Chronic lymphocytic leukemia	dim	dim	+	+	−	−
Lymphoplasmacytic lymphoma	+	+	−/+	−/+	−	−
Mantle cell lymphoma	+	+	+	−/dim	−	−
Nodal marginal zone lymphoma	+	+	−	−/+	−	−
Splenic marginal zone lymphoma	+	+	−/+	−/+	−	−/+
Follicular lymphoma	+	+	−	−/+	+/−	−
Hairy cell leukemia	+	+	−	−	−	+
B-cell prolymphocytic leukemia	+	+	−/+	−	−	−

sIg, xxx.

light-chain dim, $CD5^+/CD23^+$), a wide differential diagnosis of other B-cell hematologic malignancies needs to be considered (Table 24-1). The leukemic phase of mantle cell lymphoma is an important consideration and can be evaluated by FISH analysis for t(11;14).

The International Workshop on Chronic Lymphocytic Leukemia (iwCLL) recently published updated guidelines for the diagnosis, indications for treatment, and response assessment of CLL. The guidelines require a peripheral blood B-cell count of $\geq 5 \times 10^9$/L to establish a diagnosis of CLL in a patient with a documented CLL immunophenotype monoclonal B-cell population. Patients with a similar clonal B-cell population whose B-cell count is $<5 \times 10^9$/L are considered to have the small lymphocytic lymphoma variant of the disease if they have lymphadenopathy or splenomegaly on physical examination or computed tomographic (CT) scanning, or if they have a mass with the same clonal B cells. Patients with a circulating monoclonal B-cell population with CLL immunophenotype who do not meet these criteria are considered to have clinical MBL. Assessing the B-cell counts in the peripheral blood requires quantitative-flow cytometric immunophenotyping.

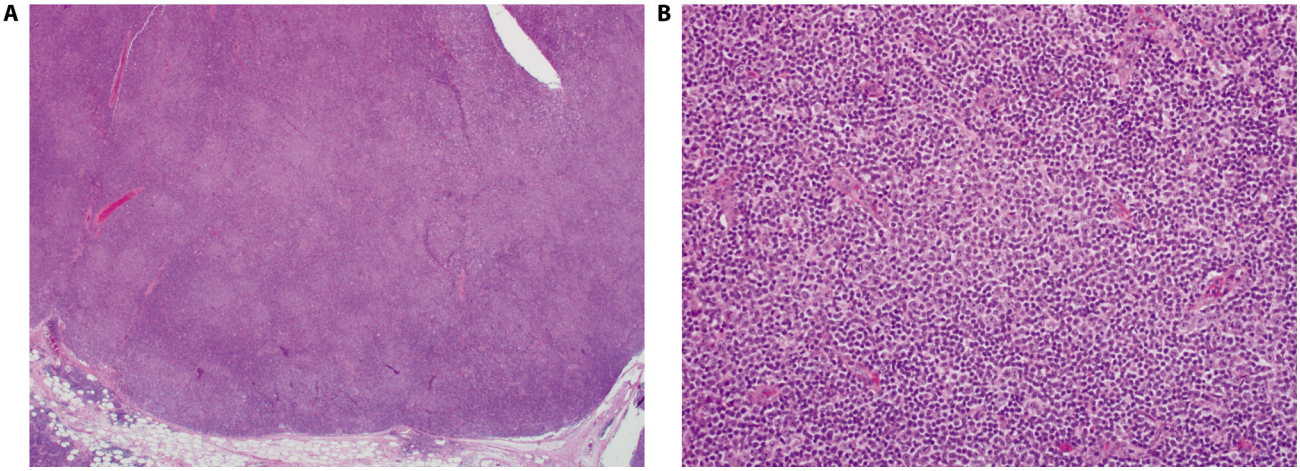
Lymph node biopsy

If a lymph node biopsy specimen shows SLL, there may or may not be detectable monoclonal B cells on peripheral blood flow cytometry. Patients who require a lymph node biopsy should, preferably, have an excisional biopsy or core biopsy for a less accessible node. Fine-needle aspiration should be avoided because it does not provide adequate tissue for architectural analysis of the lymphoid tissue. The pathognomonic characteristic of CLL/SLL is proliferation centers (pseudofollicles) (Figure 24-2).

Bone marrow study

Bone marrow study is rarely required for the diagnosis of CLL. Lymphoid tissue is preferable to bone marrow for diagnostic purposes in patients with a nondiagnostic flow cytometry immunophenotype. Bone marrow studies can be helpful in assessing the etiology of cytopenias found in conjunction with the diagnosis of CLL but are otherwise not required outside of the setting of therapy.

Figure 24-2 Section of lymph node (hematoxylin and eosin stain) from a patient with CLL. (A) Low-magnification photomicrograph (×20) showing proliferation centers (pseudofollicles). (B) High-magnification photomicrograph (×400) of a proliferation center showing central large lymphocytes rimmed by small lymphocytes.



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Imaging

Baseline imaging studies, such as CT scans or positron emission tomographic (PET) scans, are not necessary for most CLL patients at diagnosis. For most patients not receiving therapy, serial imaging is not helpful with the potential exception of patients who have bulky abdominal adenopathy and are without peripheral adenopathy. For these patients, serial imaging can be used to monitor disease progression.

Differential diagnosis

The differential diagnosis of leukemic-phase B-cell malignancies with small- to moderate-sized circulating lymphocytes with mature morphology (chronic B-cell lymphoproliferative disorders) includes CLL, mantle cell lymphoma, splenic marginal zone lymphoma, nodal marginal zone lymphoma, lymphoplasmacytic lymphoma, hairy cell leukemia, and B-cell prolymphocytic leukemia. These B-cell lymphoproliferative disorders can have distinct immunophenotypes (Table 24-1), but a definitive diagnosis can require additional testing (eg, FISH for t(11;14) for mantle cell lymphoma; MyD88/CXCR4 mutation analysis for Waldenström macroglobulinemia/lymphoplasmacytic lymphoma) or a diagnostic lymph node biopsy.

Staging

Clinical staging using clinical evaluation and the complete blood count (Table 24-2) are useful for classifying patients and identifying the small subpopulation of patients with advanced-stage disease who require therapy at the time of diagnosis. As noted previously, CT or PET/CT scan results are not used for clinical staging.

Table 24-2 Clinical staging

	Binet classification		Rai classification	
Stage	Definition	Risk group	Stage	Definition
A	<3 lymphoid areas	Low	0	Lymphocytosis only
B	>3 lymphoid areas	Intermediate	I	Lymphadenopathy
			II	Hepato- or splenomegaly
C	Hemoglobin <10 g/dL or platelets $<100 \times 10^9$/L	High	III	Hemoglobin <11 g/dL
			IV	Platelets $<100 \times 10^9$/L

KEY POINTS

- Flow cytometry is the gold standard for establishing the presence of clonal B cells with the CLL phenotype.
- The iwCLL criteria for the diagnosis of CLL require an absolute B-cell count of at least 5×10^9/L.
- A FISH probe for t(11:14) can help distinguish mantle cell lymphoma from CLL.
- A bone marrow biopsy is not required to diagnose CLL.

Risk stratification

Patients with CLL have a highly variable clinical course and outcome. Although the median time from diagnosis to first treatment is 5 to 7 years and median survival is >10 years, the wide ranges for these parameters limit the clinical utility of these data to plan patient treatment and provide accurate prognostic estimates. Because most patients with CLL are now diagnosed with earlier-stage disease, there is an important need for better prognostic markers. The most useful prognostic markers available use the biological characteristics of the patient's CLL cells.

Genetic analysis

CLL is characterized by recurrent genetic abnormal findings that can be used to predict disease biology. The most commonly used analysis is FISH, which is a reliable, widely available, and a relatively sensitive method of detecting specific chromosomal abnormal findings in interphase cells. This methodology has been complemented by the clinical availability of conventional-sequencing methods to detect abnormal findings in individual genes of interest. The methodology will likely be further expanded by the ability of next-generation sequencing (NGS) and array-based technologies, including CLL-specific mutation panels to provide rapid and affordable gene testing in the near future. This discussion focuses on methodologies that are currently clinically available.

Karyotype analysis is a useful method of detecting chromosomal defects in dividing cells. Its ability to provide genetic information for CLL patients is limited by the low level of cell division in CLL cells, especially from patients with earlier-stage disease. CLL cells can be induced to divide in vitro using mitogens and Toll-like receptor agonists, but these methods are not universally available. Complex karyotype (3 or more cytogenetic abnormal findings) on stimulated karyotype has been shown to indicate more aggressive disease in CLL and in many cases inferior responses to therapy. Stimulated karyotype, when available, can be a helpful adjunct to FISH testing.

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FISH analysis provides an accessible method, using specific probes, for testing CLL cells for commonly recurring chromosome defects. The prognostic value of these data has been extensively studied, and a hierarchical approach to ranking risk is clinically useful. Currently used genetic profiles use probes for 17p13 (*TP53* locus), 11q22.3 (*ATM* locus), trisomy 12, and 13q14 (*miR15A* and *miR16-1* loci). The hierarchical stratification for risk of disease progression is 17p13 deletion > 11q22.3 deletion > trisomy 12 > 13q14 deletion. Although this methodology is currently being modified by the addition of data from gene sequencing, the model continues to have clinical utility. Inclusion of a probe for 14q32 (*IGH* locus) can be useful for discrimination between CLL and mantle cell lymphoma in leukemic phase. In addition, translocations involving idiopathic guttate hypomelanosis do occur in a small subpopulation of patients with CLL and are associated with an adverse prognosis.

Data from FISH analysis are limited by the probe set and the sensitivity of the assay. Most laboratories analyze all nucleated cells in the submitted sample. In early-stage CLL, when the percentage of CLL cells in a blood specimen can be low, subclonal populations with a specific genetic defect can be present at a percentage below the detection threshold of FISH analysis (generally ~5%). In most patients, peripheral blood is the preferred sample for analysis. Bone marrow aspirates usually contain a large number of nucleated red blood cell (RBC) precursors that decrease assay sensitivity.

Gene sequencing has considerably improved the precision of analysis of genetic defects in the DNA damage-repair pathway in CLL. 17p13 deletion resulting in loss of 1 allele of *TP53* and 11q22.3 deletion resulting in loss of 1 allele of *ATM* usually affect only 1 chromosome, and the consequences of these deletions depend largely on the functional integrity of the remaining allele of *TP53* or *ATM*, respectively. Patients with 17p13 deletion (~5% to 10% of CLL at diagnosis, but more common in later disease stages) have ~80% rate of dysfunctional mutations in the remaining *TP53* allele, which leads to loss of p53 function in those cells. In addition, disruption of p53 function in CLL can occur because of dysfunctional mutations in *TP53* in the absence of 17p13 deletion in ~5% of patients with CLL. These mutations can result in loss of p53 function because they are biallelic, associated with uniparental disomy, or because the gene product is dominant-negative and thus inhibits the activity of remaining normal p53. Patients with 11q22.3 deletion (~15% to 20% of CLL at diagnosis) have ~30% rate of dysfunctional mutations in the remaining *ATM* allele, which results in loss of ATM function and a poor prognosis. Patients with 11q22.3 deletion that retain a wild type *ATM* have a better prognosis than patients with loss of ATM function, but the former still have an inferior outcome compared to most patients with a monoallelic dysfunctional *ATM* mutation. This suggests that the 11q22.3 deletion results in loss of additional genes (eg, *BIRC3*) that can have adverse effects on prognosis.

Genome-wide sequencing analysis of CLL has considerably improved our understanding of the molecular genetics of CLL. These studies identified several additional genes, including *NOTCH1* and *SF3B1* with recurrent mutations in CLL. Activating mutations of *NOTCH1* are detected in ~10% of patients with CLL at diagnosis, and these patients have a more aggressive disease and a significantly increased risk of transformation to diffuse large B-cell lymphoma (DLBCL). Dysfunctional mutations in the gene coding for the splicing factor 3b subunit (*SF3B1*) of the spliceosome occur in ~10% of CLL patients at diagnosis and are associated with decreased duration of response to therapy and decreased OS.

Next-generation sequencing for *TP53* mutations is clinically available and covers >90% of known defects in CLL. Use of this assay can increase the detection of *TP53* disruption in CLL at diagnosis and is recommended by iwCLL guidelines prior to the initiation of therapy. Sequencing analysis is also available for analysis of *NOTCH1* and *SF3B1* mutations in patients with CLL; however, it is not generally recommended outside of a clinical trial because of limited clinical utility.

Clonal evolution and architecture

The CLL cell population frequently contains genetically defined subclones with the potential to expand and alter the course of the disease. Serial analysis with FISH showed that the apparent rate of detection of new subclones (clonal evolution) in an initially untreated CLL population was ~5% per year. Subsequent studies using considerably more sensitive (<1% allele frequency) NGS methods and array comparative genomic hybridization studies have shown a high rate of small subclones of cells with adverse genetic defects in previously untreated CLL patients. These data suggest that progression of CLL can be associated with clonal evolution where the architecture evolution results in subclone emergence with unfavorable genetic features. The role of evaluation of clonal complexity of the CLL cell population in clinical management is currently being investigated.

BCR analysis and stereotype

The BCR signaling essential for CLL cell survival and proliferation (Figure 24-3) can be modulated by IGHV somatic hypermutation and stereotype status. IGHV somatic hypermutation and VH family usage can be determined by standard sequencing in the clinical laboratory

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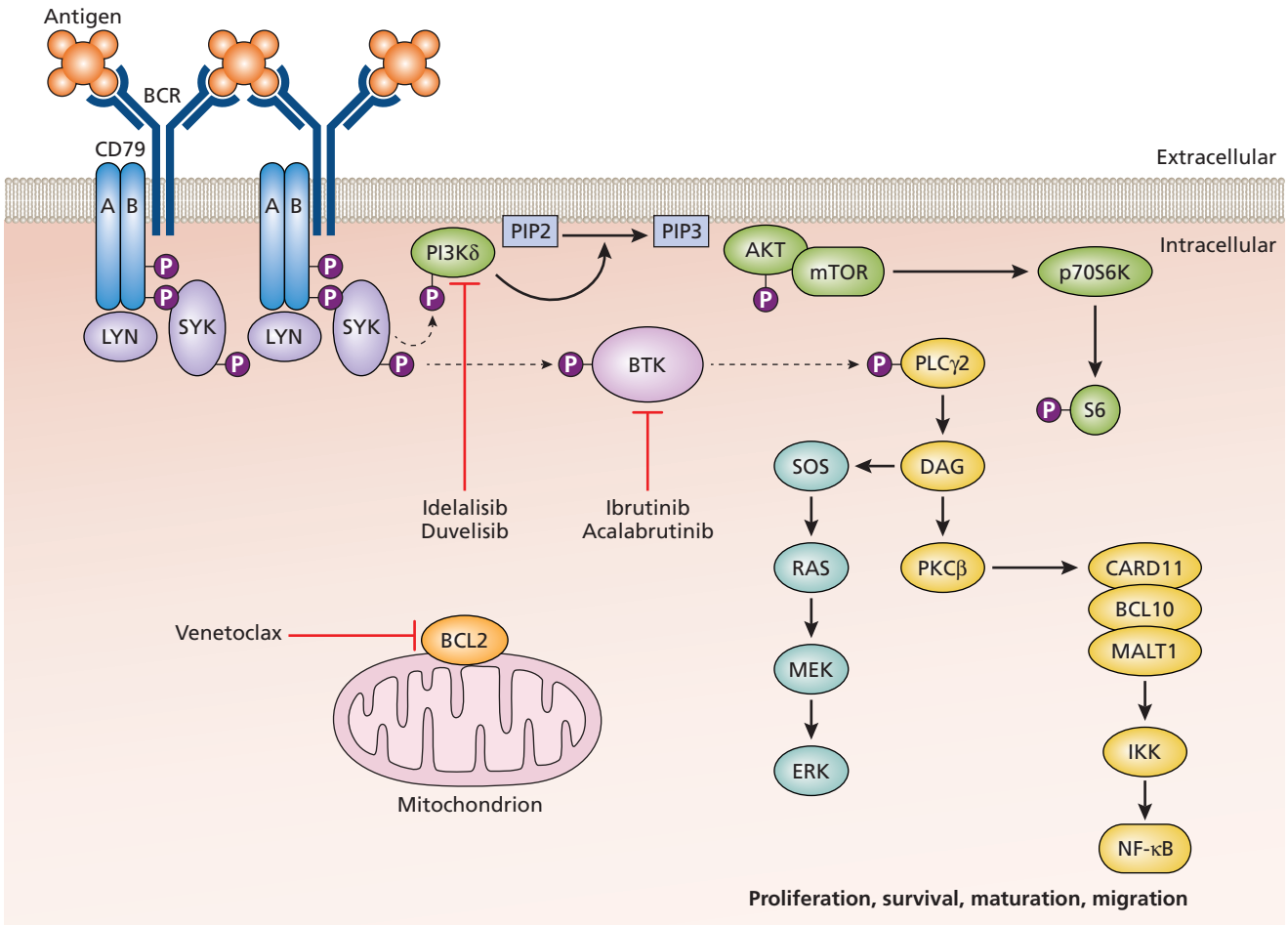

Figure 24-3 The B-cell receptor comprises the idiotypic immunoglobulin and accessory signaling molecules Igα (CD79A) and Igβ (CD79B). BCR activation induces signaling via a series of molecules to activate transcription factors (eg, NF-κB) that promote cellular survival and proliferation. Signaling requires phosphorylation (P in purple circles) by protein kinases (pink symbols) and the lipid kinase PI3Kq (green symbol). Sites of pathway inhibition by targeted kinase inhibitors are shown. Adapted from Wiestner A, *Hematology (Am Soc Hematol Educ Program)*. 2014;2014:125-134.

and does not change during the course of disease in CLL. Somatic hypermutation with gene sequence having <98% identity to germ line (mutated, ~55% of patients) is generally associated with less aggressive disease and longer survival compared to patients with ≥98% identity to germ line (unmutated, ~45% of patients). Exceptions to this finding are patients with IGHV using VH3-21, some of whom have a poorer prognosis irrespective of mutation status.

Analysis of the immunoglobulin gene repertoire in CLL cells has contributed to a better understanding of the molecular pathogenesis of CLL. The recognition of a biased IGHV gene repertoire in CLL, distinct from typical B cells, and the discovery of specific antigen-binding sites among unrelated cases established the importance of antigen in the selection of CLL progenitor cells. Antigen-binding sites (VH complementarity-determining region 3 [CDR3]) with high homology to previously described sites occur in ~20% to 30% of patients. These quasi-identical or stereotyped BCR can be classified into 1 of 19 major subsets, each of which has prognostic implications. The clinical implication of the stereotype on treatment of CLL patients continues to be defined.

Prognostic markers of CLL cells

CLL cells can be analyzed for proteins that are differentially expressed in populations of patients with a higher or lower risk of CLL progression.

ZAP70 is expressed by some normal and malignant B-cell findings during differentiation and maturation, and it has a role in BCR signaling in CLL cells. ZAP70 assays were initially proposed as surrogate markers for IGHV

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mutation. However, subsequently studies showed a poor correlation (~70%) between these parameters, which is not clinically useful. Higher levels of expression of ZAP70 are, however, an independent marker of more aggressive CLL. Clinical use of this prognostic factor has been limited because accurate quantification of intracellular proteins by flow cytometry in clinical laboratories is technically difficult, and its use has largely fallen out of favor.

CD38 is a multifunctional surface molecule expressed by hematopoietic cells, including B cells during maturation. CD38 is ligand of CD31 (PECAM1), has enzymatic activity important for calcium metabolism, and can interact with the BCR/CD19 complex in B cells. CD38 expression by circulating-CLL cells correlates with the rate of cellular turnover. Population studies show that higher levels of CD38 correlate with a more aggressive disease and poorer outcome. However, the level of CD38 is not constant in patients with CLL, and there is difficulty determining the best cut-off for this continuous variable for risk stratification.

CD49d is the α_4-integrin subunit that can associate with CD29 to form the $\alpha_{4\beta1}$-integrin (VLA-4). VLA-4, which is expressed by B cells including CLL, binds VCAM-1 (expressed by endothelial cells and bone marrow stromal cells) and the extracellular matrix molecule fibronectin. VLA-4 has an important role in trafficking of hematopoietic cells through the endothelium required to home to the lymph nodes and bone marrow. In CLL patients, increased CD49d expression is associated with a shorter time to first treatment and a poorer OS. Expression levels of CD49d are reported to be stable over time in individual patients. Although CD49d is the strongest flow-based predictor of OS, the availability and reporting of CD49d in clinical practice is variable.

β_2-Microglobulin (B2M) is a polypeptide associated with human leukocyte antigen (HLA) I on the cell membrane. Serum levels can be increased in several hematologic malignancies, including CLL. Increased serum B2M levels that exceed twice the upper limit of normal results are associated with increased CLL tumor burden, shorter treatment-free survival, and OS with chemoimmunotherapy. B2M is metabolized in the kidneys and levels are increased in patients with renal impairment.

Lymphocyte doubling time (LDT) is an estimate of time required for a patient's absolute lymphocyte count (ALC) to double. A clinically useful value requires a baseline ALC of $>15 \times 10^9$/L and 2 weekly counts over a period of at least 2 months. The LDT should then be calculated using linear regression. The initial studies in small patient cohorts reported in the 1980s concluded that a LDT of <12 months was associated with poorer prognosis. However, ALC is a labile parameter that is poorly predictive of the total tumor burden in CLL (<10% of CLL cells are in the circulation at any one time), and LDT should not be used as the sole parameter to predict a patient's prognosis or initiate treatment.

Prognosis at diagnosis

Developing an accurate and accessible prognostic examination system in newly diagnosed early-intermediate stage CLL patients has been challenging because of our rapidly changing understanding of the biology of the disease, the large number of potential prognostic factors, limitations of some of the published studies, and the indolent nature of the disease. The indolent nature of CLL frequently makes the results of clinical studies of novel prognostic factors redundant before they are completed. In addition, factors, such as *TP53* disruption, which occurs in <10% of patients at diagnosis, are detected at low frequency with currently used clinical assays but are subsequently responsible for a disproportionate number of patients with a more aggressive disease and poor outcome.

A prognostic model combining genetic, biochemic, and clinical parameters, called the CLL-International Prognostic Index (CLL-IPI), has been developed (Table 24-3). After analysis of 27 baseline prognostic factors, the CLL-IPI Working Group determined that there are 5 independent prognostic markers for OS in CLL: TP53 (no abnormal findings versus 17p13 deletion/TP53 mutations/both); IGHV mutational status (mutated versus unmutated); serum B2M concentration (≤3.5 mg/L versus >3.5 mg/L); clinical stage (Binet A or Rai 0 versus Binet B-C or Rai I-IV]); age (≤65 years versus >65 years). Each marker was assigned a weighted risk score, and the combined score may allow for a more targeted treatment of patients with CLL. The utility of the CLL-IPI in the time to treatment of CLL patients has been clearly established; however, the utility in outcome prediction for patients receiving targeted therapies has not been fully validated.

Table 24-3 CLL-International Prognostic Index

Variable	Adverse factor	Score
Age	>65 y	1
Clinical stage	Binet B/C or Rai I-IV	1
17p13 deletion and/or TP53 mutation	Deleted and/or mutated	4
IGHV mutation status	Unmutated	2
B2M level (mg/L)	>3.5 mg/L	2

Prognostic scores range from 0 to 10 and identify 4 risk groups with significantly different rates of OS at 5 y ($P < 0.001$ for all): low-risk patients (score 0-1), 93.2% (95% CI, 90.5-96.0); intermediate risk (score 2-3), 79.3% (95% CI, 75.5-83.2); high risk (score 4-6), 63.3% (95% CI, 57.9-68.8); and very high risk (score 7-10), 23.3% (95% CI, 12.5-34.1).

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KEY POINTS

- *TP53* disruption in CLL is associated with inferior prognosis.
- Patients with IGHV somatic hypermutation have superior survival compared to those without somatic hypermutation (unmutated).
- IGHV mutation status, FISH, and TP53 mutation analysis should be undertaken prior to initiation of therapy.

Management

Management of CLL has evolved rapidly over the past decade because of more accurate and earlier diagnosis, better risk stratification, recognition of complications and methods to prevent them, and the development of highly effective targeted therapies and immunotherapy.

At present, there is no proven benefit to early treatment of patients with CLL. However, earlier diagnosis does allow implementation of an active management plan to prevent complications of disease, early management of complications, and appropriate timing of treatment. Patients need to be well educated about their disease, the clinical manifestations of disease progression and complications, precautionary measures (see "Complications of CLL" later in this chapter), and measures to improve general fitness. The interval of patient follow-up can be determined by using clinical monitoring and risk-factor analysis. The indications for initiation of treatment of progressive disease in both previously untreated patients and those with relapsed/refractory disease are based on the iwCLL guidelines (Table 24-4).

Goals of treatment should be considered for each patient. These goals may include improvement in disease-related symptoms, quality of life, and prolongation of survival. As discussed in the following, current therapies are achieving deeper remissions, including minimal residual disease (MRD) undetectable responses. Such responses may significantly delay relapse, providing the rationale for MRD endpoints in ongoing clinical trials in an attempt to improve survival.

Monoclonal B-cell lymphocytosis

Patients with an incidental detection of a monoclonal B-cell population are classified as CLL-type, atypical-CLL-type, and non-CLL-type, based on flow cytometry. All patients should have an examination for symptoms and evidence of lymphadenopathy and visceromegaly. Those with CLL-type MBL are further divided into low-count (<50 clonal cells/μL) or

Figure 24-4 Initial treatment of progressive CLL. (A) Initial selection of therapy for patients with progressive CLL should be based on patient age/fitness and the biology of the disease. Patients with aberrant p53 function based on FISH analysis for 17p13 deletion or sequencing of *TP53* (disrupted *TP53*) should be treated with targeted therapy and not chemoimmunotherapy. Patients without disrupted *TP53* and mutated IGHV may be treated with FCR CIT or with targeted therapy like a BTK inhibitor or venetoclax with or without a CD20 monoclonal antibody. BR, bendamustine and rituximab.

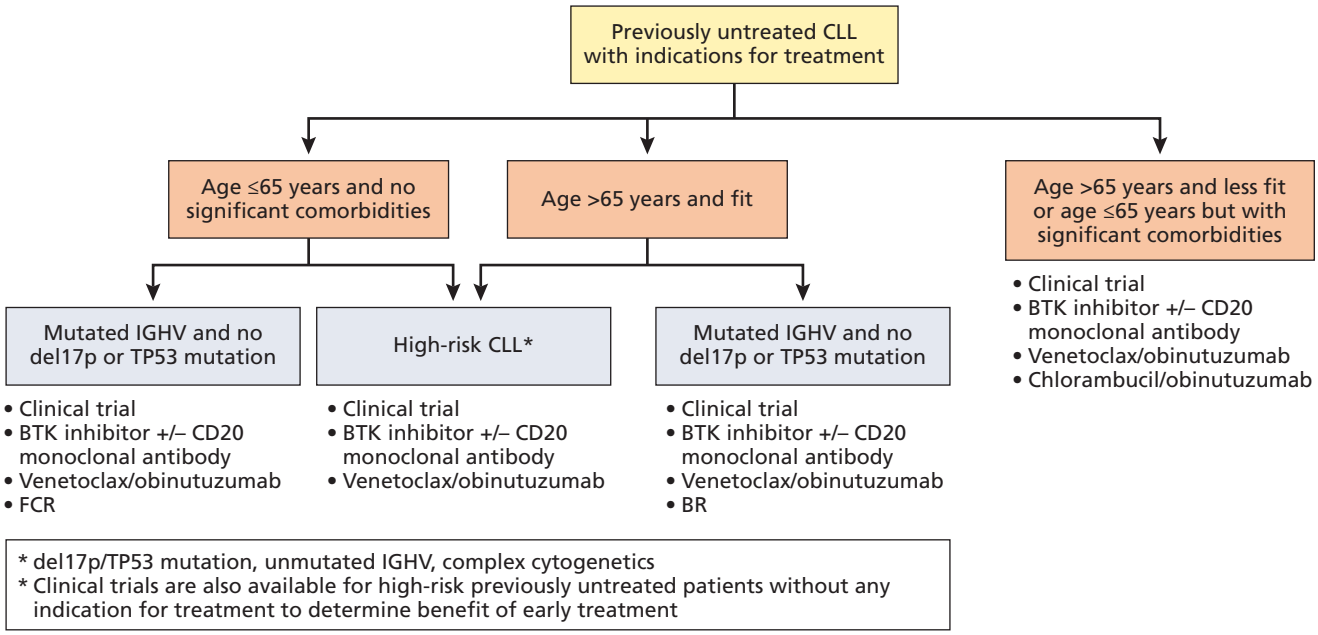
Previously untreated CLL with indications for treatment
Age ≤65 years and no significant comorbidities
Age >65 years and fit
Age >65 years and less fit or age ≤65 years but with significant comorbidities
Mutated IGHV and no del17p or TP53 mutation
High-risk CLL*
Mutated IGHV and no del17p or TP53 mutation
• Clinical trial
• BTK inhibitor +/– CD20 monoclonal antibody
• Venetoclax/obinutuzumab
• FCR
• Clinical trial
• BTK inhibitor +/– CD20 monoclonal antibody
• Venetoclax/obinutuzumab
• Clinical trial
• BTK inhibitor +/– CD20 monoclonal antibody
• Venetoclax/obinutuzumab
• BR
• Clinical trial
• BTK inhibitor +/– CD20 monoclonal antibody
• Venetoclax/obinutuzumab
• Chlorambucil/obinutuzumab
* del17p/TP53 mutation, unmutated IGHV, complex cytogenetics
* Clinical trials are also available for high-risk previously untreated patients without any indication for treatment to determine benefit of early treatment

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Table 24-4 General indications for initiation of treatment in CLL (iwCLL 2018)

Indication	Description	Precautions
Bone marrow failure	Anemia (eg, Hb <10 g/dL) and/or thrombocytopenia (eg, <100 × 10^9/L and dropping)	Require bone marrow study to confirm bone marrow failure
Symptomatic disease	Unintentional weight loss >10% during the past 6 mo	Exclude other causative pathologies (eg, sleep disorder, depression, hypothyroidism, chronic infection/inflammation)
	Fatigue*: ECOG performance status ≥2; cannot work or perform usual activities	
	Fevers >38°C for ≥2 wk without evidence of infection	
	Night sweats for >1 mo without evidence of infection	
Splenomegaly	Massive (>6 cm below the left costal margin) or symptomatic (abdominal distention, early satiety, pain) or progressive	
Lymphadenopathy	Massive (>10 cm in longest diameter) or symptomatic or progressive	Exclude infectious lymphadenitis and transformation to diffuse large B-cell lymphoma
Progressive lymphocytosis	Increase in absolute lymphocyte count of >50% in 2 mo or lymphocyte doubling time of <6 mo	Baseline ALC for calculation of LDT must be >30 × 10^9/L. LDT needs to be determined by using multiple serial ALC counts (2 weekly ALC for >3 mo) to perform linear regression analysis. All other potential causes of changes in ALC (eg, infection, recent use of corticosteroids) need to be excluded. ALC alone should not be used as an indication for treatment.
Autoimmune complications	Anemia or thrombocytopenia poorly responsive to corticosteroids	
Extranodal involvement	Symptomatic or functional (eg, skin, kidney, lung, spine)	

*Use of fatigue as a sole indication for treatment of patients with CLL requires a careful examination and exclusion of all alternative etiologies.

high-count (>2000 clonal cells/μL). Patients with atypical or non-CLL-type should be monitored intermittently for progression to a hematologic malignancy; however, the optimal monitoring strategy is not established. Those patients with low-count CLL-type MBL, without other signs of disease, may be at higher risk for infections than the general population, but otherwise they do not appear to have a clinically significant risk of progressing to overt hematologic malignancy. Patients with high-count CLL-type MBL have an annual 1% to 2% risk of progression to CLL, and they have a higher incidence of infections and secondary cancers. These patients should be monitored initially at least twice per year.

Initial treatment of progressive CLL

Initial therapy for CLL has undergone dramatic transformation over the past few years (Figure 24-4). Whereas chemoimmunotherapy used to be standard for the majority of patients, newer targeted agents have become the standard of care for almost all patients with previously untreated disease. Despite the efficacy of these therapies, evaluation of CLL biology as well as patient fitness is required to deliver optimal therapy.

Indications for treatment

Patients are considered to have active progressive disease requiring treatment if they have symptomatic disease, rapid disease progression, or bone marrow failure as per iwCLL guidelines (Table 24-4). Although this remains an area of active clinical investigation, there is currently no role for early therapy.

Pretreatment evaluation

Before initiation of therapy, patients should be examined for fitness, genomic disease characteristics, and disease burden.

Physical fitness should be determined using a minimum of standard evaluations of organ function (eg, estimated creatinine clearance) and performance status. Fitness-for-treatment should be assessed on an individual basis rather than by using chronological age alone. The role of

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more sophisticated methods of quantifying comorbidity and physical fitness, such as the cumulative illness rating scale, are still investigational. Decreased fitness caused by potentially reversible CLL-induced causes (eg, fatigue and symptomatic anemia) need to be carefully excluded from this examination. Fit patients should have an Eastern Cooperative Oncology Group (ECOG) performance score (PS) of 0 or 1, no evidence of significant organ impairment, and no major comorbidity. Patients who are unfit, with PS ≥3, major organ failure, or limiting comorbidity should be considered for supportive and palliative care as well as for therapy with targeted agents. Toxicity of particular agents should be considered carefully when choosing therapy for patients with intermediate or low fitness.

As detailed previously, *TP53* disruption by deletion and/or mutation (17p13 deletion/TP53^{mutation}) predicts poor response to chemoimmunotherapy and is an indication for alternative treatment approaches when treatment is indicated. CLL patients can have long intervals between diagnosis and treatment during which their CLL biology can be altered either by subclonal selection or by new mutations (clonal evolution). In patients without a previously demonstrated *TP53* disruption, a FISH panel, including a probe for 17p13 and *TP53* sequencing, should be performed within 6 months prior to initiation or change of treatment. The emergence of other mutations that can be detected by FISH (eg, del11q23) are also important and may influence choice of therapy. Therefore, we advocate obtaining a FISH panel as well.

Evaluation of CLL disease burden before initiation of treatment is useful for planning therapy and evaluating response. Patients require a clinical examination of disease burden based on symptoms and physical examination with bidimensional measurement of the largest lymph node in the cervical, axillary, and inguinal/femoral regions on each side; measurement of the size of the liver; and measurement of the spleen (measured in centimeters below the costal margin at rest and at maximal inspiration in the midclavicular line). Imaging is required to determine the size of the nonpalpable lymph nodes in the chest, abdomen, and pelvis when using therapies such as venetoclax—where it is required to determine tumor lysis risk—as well as in clinical trials. CLL cells are usually not fluorodeoxyglucose avid, and PET scans should not be routinely used for CLL evaluation prior to initiation of therapy or for response assessment unless Richter transformation is suspected.

Pretherapy precautions

Use of monoclonal antibody therapy and myelosuppressive drugs increases the risks of reactivation of latent infections. CLL patients should be tested for evidence of infection with hepatitis B and hepatitis C viruses before initiation of chemotherapy, Bruton's tyrosine kinase (BTK) inhibitors, or monoclonal antibodies. Patients at high risk of reactivation (National Comprehensive Cancer Network [NCCN] guidelines can be consulted to define this population) should receive antiviral therapy to minimize this risk. Patients could also benefit from antiherpes virus and anti*Pneumocystis* prophylaxis with some regimens; although, the value of these precautions is not proven. Effective therapy for CLL can cause rapid cytotoxicity of CLL cells with toxic consequences, including tumor lysis syndrome. Prophylactic allopurinol and hydration together with appropriate monitoring are suggested particularly in patients with a high burden of disease at the start of therapy.

BTK inhibitors in treatment-naïve CLL

BTK is an important component of the B-cell receptor signaling pathway (Figure 24-3) expressed in hematopoietic tissue, except T cells and plasma cells. The first in class covalent BTK inhibitor ibrutinib was the first targeted therapy approved in treatment-naïve CLL, and it heralded the shift from chemoimmunotherapy to targeted treatment in this disease. Currently, there are 2 BTK inhibitors that have received United States Food and Drug Administration (FDA) approval for the initial treatment of CLL: ibrutinib and acalabrutinib. Both drugs are orally administered and bind covalently to a cysteine residue near the enzymatic site of BTK, resulting in irreversible inhibition. Therapy is frequently associated with an early increase in lymphocytosis owing to redistribution that does not affect the response to therapy, usually peaks after 1 month of therapy, and subsequently slowly declines. The median time to resolution of lymphocytosis on ibrutinib therapy is 19 weeks, but prolonged lymphocytosis up to 124 weeks has been seen in patients with ongoing treatment responses. Treatment-related lymphocytosis is a class effect associated with use of drugs that inhibit BCR-pathway signaling and does not require specific management.

Ibrutinib

Ibrutinib was approved for frontline treatment of CLL based on the RESONATE 2 study, which compared ibrutinib to chlorambucil in previously untreated patients aged 65 years and older. Ibrutinib improved both progression-free survival (PFS) and OS compared with chlorambucil. Long-term follow-up has revealed a 5-year PFS of 70% with ibrutinib in this study. Ibrutinib has also been compared with more effective chemoimmunotherapy regimens in the National Clinical Trials

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Network trials Alliance 041202 and ECOG 1912 study. In A041202, ibrutinib was compared with ibrutinib plus rituximab and bendamustine plus rituximab in patients aged 65 and older. Both ibrutinib-containing regimens prolonged PFS over chemoimmunotherapy, and there was no difference in PFS between ibrutinib alone or in combination with rituximab. In E1912, ibrutinib plus rituximab was compared with fludarabine/cyclophosphamide/rituximab (FCR) in patients under the age of 70 who did not have del(17p). The ibrutinib and rituximab combination prolonged both PFS and OS when compared with FCR. In both of these trials, the benefit to ibrutinib over chemoimmunotherapy was most prominent in patients with unmutated IGHV. Longer-term follow-up will be required to see whether patients with low-risk mutated IGHV have a similar benefit.

Acalabrutinib

Acalabrutinib was approved for frontline treatment of CLL based on the ELEVATE TN study, which compared acalabrutinib alone and acalabrutinib plus obinutuzumab to chlorambucil plus obinutuzumab. PFS was prolonged for either acalabrutinib alone or in combination compared with chemoimmunotherapy. There was a trend toward improved PFS for acalabrutinib plus obinutuzumab versus acalabrutinib alone in a post hoc exploratory analysis; however, long-term follow-up will be needed to determine if this benefit is clearly observed.

Toxicities

BTK inhibitors have unique toxicities compared with chemotherapy in CLL. Serious toxicities, including atrial fibrillation, bleeding, and hypertension, are observed at low frequency. Other therapies including those for gastroesophageal reflux disease, arthralgias/myalgias, and diarrhea are commonly seen as well. Infections are commonly observed; however, infection rate compared with other therapies is not clearly increased, and risk of serious infection decreases with prolonged administration. Many toxicities, especially cardiac toxicities, are more common with ibrutinib than acalabrutinib. The current treatment paradigm is for indefinite dosing of BTK inhibitors in CLL, so toxicity management is paramount to maintain treatment efficacy.

Venetoclax in treatment-naïve CLL

Venetoclax is an orally active, targeted small-molecule inhibitor of the antiapoptotic molecule BCL2 that is expressed at high levels in CLL cells. Based on the CLL 14 study observing treatment-naïve CLL, venetoclax is administered in combination with the anti-CD20 monoclonal antibody obinutuzumab for a total venetoclax duration of 1 year. In this trial, venetoclax plus obinutuzumab was compared with chlorambucil plus obinutuzumab in previously untreated patients with CLL and coexisting medical conditions. Venetoclax plus obinutuzumab prolonged PFS versus chemoimmunotherapy. At 3 years of follow-up, 82% of patients treated with venetoclax were progression-free compared with 50% of chemoimmunotherapy treated patients. Undetectable MRD, where no CLL can be detected to a depth of <1 CLL cell/10,000 leukocytes, was seen in the bone marrow of 57% of patients treated with venetoclax plus obinutuzumab.

Venetoclax is generally well tolerated in CLL. Toxicities of concern with the venetoclax plus obinutuzumab regimen include neutropenia and tumor lysis syndrome (TLS). TLS can be seen with either venetoclax or obinutuzumab as a single agent as well. With venetoclax, rapid TLS was an early identified significant toxicity in CLL. Risk has been mitigated in most patients through strict pretreatment examination of high-risk patients based on lymph node size and lymphocyte count, ramp-up dosing schedule, and hospitalization of patients at high risk for TLS. Ramp-up dosing for venetoclax in CLL consists of weekly escalation using doses of 20 mg, 50 mg, 100 mg, 200 mg, and then 400 mg. On dose escalation days, laboratory monitoring for TLS occurs predose and postdose, depending on the risk of TLS and dose level (DL) of escalation.

Chemoimmunotherapy in treatment-naïve CLL

As a reaction to head-to-head comparisons that show superiority of targeted agents, chemoimmunotherapy is not recommended for most patients with treatment-naïve CLL. However, long-term follow-up of trials of FCR in CLL has demonstrated that a subset of patients with IGHV mutated disease and without high-risk cytogenetic abnormal findings can have prolonged responses >10 years, which may represent a cure. Toxicities of FCR, including short-term myelosuppression, infectious complications, and long-term risk of therapy-related MDS/AML, make this a regimen best suited for young (≤65 years) and healthy patients with IGHV mutated disease and without TP53 or ATM abnormal findings. Current studies are focused on limiting chemotherapy and/or adding novel agents in an effort to limit toxicity but still achieve a potential cure.

Besides FCR, other chemoimmunotherapy regimens, including bendamustine plus rituximab and chlorambucil plus obinutuzumab, are effective in CLL and can be considered for patients who have a contraindication to

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targeted therapy. Neither of these agents have been shown in trials to have the potential for disease cure that is seen with FCR.

MRD assessment

With time-limited therapies using chemotherapy or venetoclax, the presence of MRD at the end of therapy has been shown to correlate with shorter PFS. These data are based primarily on studies using flow-based MRD with a sensitivity of 10^{-4} (or 1/10,000 leukocytes). NGS methods are now available that offer increased sensitivity to 10^{-6} (or 1/1,000,000 leukocytes). Currently, data do not exist to support using end-of-therapy or midtherapy MRD status to guide treatment decisions, but this is the subject of current clinical trials. Therefore, at this time, MRD assessment can be performed at the end of a finite therapy for prognostic assessment. There is no indication to perform MRD analysis in patients receiving continuous therapy (ie, BTK inhibitor).

Treatment of relapsed/refractory CLL

Patients with relapsed/refractory CLL after a fixed-duration therapy can often be safely monitored until they meet the iwCLL criteria for progressive disease detailed in Table 24-3. Pretreatment examination of relapsed/refractory patients is similar to that required prior to initial treatment and includes assessment of fitness, CLL biological risk, assessment of CLL disease burden, and screening for hepatitis B and C, depending on therapy. Chemoimmunotherapy is not recommended in the setting of relapsed/refractory CLL. For patients who received chemoimmunotherapy (CIT) as their initial therapy, options for therapy at relapse include any available novel agent. In general, if a patient starts therapy with BTK inhibitor-based therapy and if they experience disease progression during BTK inhibitor therapy, treatment can be switched successfully to venetoclax-based therapy. Patients who received venetoclax-based therapy as initial treatment can, at progression, be successfully treated with BTK inhibitor-based therapy. Retreatment with a venetoclax-based treatment can also be considered, especially in the case of a long disease-free interval after therapy discontinuation.

BTK inhibition in relapsed/refractory disease

Ibrutinib

Ibrutinib monotherapy provides a highly effective but noncurative option for patients with relapsed refractory CLL, as demonstrated in the RESONATE phase 3 where median PFS was significantly higher with ibrutinib (44 months) compared with ofatumumab (8 months) at the 6-year final analysis. In patients with relapsed/refractory CLL with very-high-risk disease (17p13 deletion/*TP53* mutation and purine analog refractory), ibrutinib has achieved high response rates (ORR ~90%). Although most of these responses were PR or PR-L (~80%) with low complete remission (CR) rates (<10%), CR rates continued to increase with ongoing therapy with a median time to CR of 21 months in one study. The duration of response is considerably better than those reported for previously-used CIT with a median PFS of 44 months. Both PFS and OS appear to be inferior in patients with 17p13 deletion as well as complex karyotype compared with those with other prognostic marker differences, including IGHV mutation status, expression of CD38 and ZAP70, and other FISH-determined genetic abnormal findings.

Patients with relapsed/refractory CLL can acquire resistance to the drug after an initial response to treatment. Transformation to diffuse DLBCL or Hodgkin lymphoma (Richter transformation) is observed in <5% of treated individuals and tends to occur within the first 6 months of therapy. Acquired resistance to ibrutinib therapy is largely because of mutations that prevent ibrutinib from inhibiting BCR signaling. Two such mutations have been described: a cysteine to serine change at amino acid 481 in BTK that prevents ibrutinib binding to the active enzymatic site and a gain of function mutation in the gene coding for PLCγ2 that results in autonomous BCR signaling. Although the total number of mutations is low, these mutations were found in 85% of heavily pretreated patients who experienced disease progression while receiving ibrutinib therapy. Disease progression on ibrutinib therapy is most frequent in patients with 17p13 deletion/*TP53* mutation as well as with complex-karyotypic abnormal findings (>1 aberration). These BCR-pathway mutations have not yet been detected in patients with CLL prior to initiation of treatment with ibrutinib, suggesting that mutations occur either because of new mutations or by selection of preexisting subclones of ibrutinib-resistant cells too small to detect by current assays. If ibrutinib is stopped because of progressive disease, rapid disease progression can occur. Therefore, for patients who have an indication for immediate therapy, it is appropriate to continue ibrutinib until an alternative therapy is started.

Ibrutinib combination therapy is being tested in clinical trials to see if deeper responses and possibly fixed treatment duration can be achieved (eg, with venetoclax). Combination with anti-CD20 monoclonal antibodies is potentially attractive because monoclonal antibodies are most effective at killing circulating-CLL cells. However, enthusiasm for these combinations is tempered by data suggesting that ibrutinib could decrease cell-mediated

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monoclonal-antibody-dependent cytotoxicity. A recent trial, involving previously treated patients, demonstrated no improvement in PFS with the addition of rituximab to ibrutinib.

Acalabrutinib

The emergence of acalabrutinib, a second generation BTK inhibitor, has also shown promise in the treatment of CLL/SLL. The phase 3 ASCEND trial examined 310 individuals with relapsed/refractory CLL randomized to receive either acalabrutinib monotherapy or, investigator's choice, idealisib plus rituximab or bendamustine plus rituximab. Notably participants had not received prior treatment with BTK inhibitors or BCL2 inhibitors but had received a median of 2 prior therapies. At median 16.1 months follow-up interval, PFS was not reached in the acalabrutinib arm with estimated PFS of 88% compared to 68% in the investigator's choice arm. Improved PFS in the acalabrutinib arm was also shown in high-risk subtypes like deletion 17p, deletion 11q, and IGHV unmutated disease. Common grade 3 or 4 toxicities observed in the acalabrutinib arm include neutropenia, anemia, thrombocytopenia, pneumonia, and 5% of individuals in the acalabrutinib monotherapy group developed atrial fibrillation. In the idelalisib plus rituximab group, common grade 3-4 toxicities included higher rates of neutropenia and diarrhea. The ELEVATE-RR phase 3 trial, comparing acalabrutinib and ibrutinib, directly demonstrated noninferior PFS with acalabrutinib to that with ibrutinib. In addition, acalabrutinib was associated with a reduced risk of atrial fibrillation.

Reversible BTK inhibitors

Reversible inhibitors of BTK have been developed in response to known resistance mechanisms involving mutations in BTK. These agents, of which many are currently in trials, bind BTK at alternate sites from the irreversible inhibitors (eg, ibrutinib and acalabrutinib) and are active in the setting of C481S mutated BTK. Furthest along in development is pirtobrutinib, which has shown an ORR of 62% in highly refractory patients with a median of 4 prior lines of therapy, including those with prior BTK inhibitor exposure. Pirtobrutinib is highly selective, and thus has minimal toxicity. This agent is currently in phase 3 clinical trials.

BCL2 inhibition in relapsed/refractory CLL

Venetoclax was initially approved by the FDA for previously treated patients with 17p13 deletion CLL and has now received broader approval in the relapsed setting. The approval is based on the phase 3 Murano trial, comparing venetoclax plus rituximab to bendamustine plus rituximab. PFS, at a median of 23.8 months, was 84.9% in the venetoclax arm versus 36.3% in the bendamustine arm. The benefit of venetoclax was observed across all subtypes, including the deletion 17p subgroup that notably had an 81% PFS at 2 years in the venetoclax arm. Venetoclax has also demonstrated a benefit in patients previously treated with either ibrutinib or idelalisib who have either become resistant to, or intolerant of, these therapies.

PI3Kδ inhibition in relapsed/refractory CLL

The PI3K p110δ (PI3Kδ) enzyme is expressed primarily in hematopoietic tissue and is especially important for B-cell maturation and survival. In CLL, PI3K activity is constitutively activated, which suggests that it could be a good target for therapy. Specific inhibitors of PI3Kδ could thus provide targeted therapy for CLL. Inhibition of PI3Kδ prevents phosphorylation of the serine/threonine kinases AKT and mTOR, resulting in decreased BCR-pathway signaling (Figure 24-3). In addition to the approved PI3K inhibitors described in the following, others, such as umbralisib, are in development and have shown promising efficacy with reduced toxicity.

Idelalisib

Idelalisib is FDA approved for CLL therapy in combination with rituximab for relapsed CLL patients with comorbidities. A randomized controlled study tested idelalisib and rituximab versus rituximab alone in CLL patients with relapsed/refractory disease and comorbidities that precluded the use of CIT. Addition of idelalisib to rituximab significantly improved ORR, PFS, and OS. A subsequent update of this study showed that response rates and PFS in the patients receiving idelalisib and rituximab were not affected by 17p13 deletion/*TP53* mutation, IGHV mutation status, or levels of ZAP70 expression. Idelalisib does have important potential toxicity that requires close treatment of patients. Gastrointestinal complications include diarrhea that can be severe and nonresponsive to motility-inhibiting drugs, severe colitis, and intestinal perforation. Hepatic toxicity includes frequent transaminitis that usually resolves on drug cessation and, less commonly, more severe hepatitis that requires intervention. Severe hepatotoxicity was noted primarily in young, previously untreated patients. Pneumonitis requiring drug cessation and treatment with corticosteroids has been reported. Additional toxicities include pyrexia, fatigue, nausea, rash, neutropenia, hypertriglyceridemia, and hyperglycemia. Idelalisib has been shown to increase the risk of infection, including cytomegalovirus (CMV) infection or viremia and *Pneumocystis jirovecii* pneumonia, infections that are typically seen in immunocompromised

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patients. Careful monitoring is required. Idelalisib induces CYP3A, and so the risk of adverse drug interactions must be considered.

Duvelisib

The phase 3 DUO study established the role of duvelisib, a PI3K delta and gamma inhibitor, in the relapsed/refractory setting in 319 individuals with CLL/SLL randomized to either duvelisib or ofatumumab. Duvelisib was found to have superior PFS over ofatumumab with a median of 13.3 months versus 9.9 months (hazard ratio [HR] = 0.52, $P < 0.001$). Efficacy was also observed in high-risk deletion 17p and *TP53* mutated cases. Common grade 3 or higher toxicities in the duvelisib group were neutropenia, anemia, diarrhea/colitis, and pneumonia (14%). This led to the approval of duvelisib by the FDA for relapsed/refractory CLL/SLL.

Immunotherapy

Restoring immune surveillance and immune-based cytotoxicity capable of preventing recurrence of CLL in patients who have MRD after effective therapy can result in long-term disease control and possibly even cure. The first effective modality was reduced-intensity conditioning (RIC) allogeneic stem cell transplantation (allo-SCT) in selected patients. Chimeric antigen receptor T-cell (CAR-T) therapy is now being evaluated in clinical trials.

RIC allo-SCT is effective therapy in relapsed/refractory CLL for patients with very-high-risk disease. However, while 5-year PFS is between 35% to 40%, therapy is complicated by chronic graft-versus-host disease with treatment-related mortality of ~20%. Optimal results are achieved in younger and fitter patients with minimal residual CLL who have not had extensive prior therapy. The availability of highly effective targeted small-molecule therapies and alternative immunotherapies has reduced the enthusiasm for RIC allo-SCT in CLL, and indications for use of this therapy are currently unclear. Patients with very-high-risk CLL, who are candidates for immune therapy, should be referred for examination at a center specializing in the treatment of CLL early in the course of their disease.

CAR-T therapy

Ex vivo introduction of chimeric genes into autologous T cells using lentivirus vectors can induce "autologous" anti-CLL immunity. The chimeric gene construct code for antibody variable regions (eg, B-cell specific anti-CD19 or more CLL-specific anti-ROR1) together with immunostimulatory molecules (eg, CD3z, CD28, CD137). CAR T-cell therapies are being evaluated in ongoing clinical trials after promising initial results were observed in CLL. The largest multicenter CAR T-cell trial in relapsed/refractory CLL to date is the open-label, phase 1/2 TRANSCEND CLL 004 (NCT03331198) study of lisocabtagene maraleucel (liso-cel), a CD19-directed CAR T-cell therapy. Results from 23 of 25 evaluable patients in the phase 1 dose escalation portion of the study were recently reported. Patients with standard- or high-risk features of CLL treated with ≥3 or ≥2 prior therapies, respectively, including a BTKi in all, received liso-cel at 50×10^6 (DL1) or 100×10^6 (DL2) CAR^+ T cells. Patients had a median of 4 (range, 2-11) prior therapies (100% had ibrutinib; 65% had venetoclax), and a majority had high-risk features including mutated *TP53* and del(17p). Reassuringly, there were few grade 3 cytokine release syndrome events and there was no grade 4 cytokine release syndrome. Similarly, there were few grade 3 or 4 neurologic events. These occur primarily within the first 2 weeks after CAR T-cell therapy and are manageable with tocilizumab and steroid interventions. Rapid, deep, and durable results have been reported with 82% and 45% overall and complete responses, respectively. Of 20 MRD-evaluable patients, 75% and 65% achieved undetectable MRD in blood and marrow, respectively. Safety and efficacy were similar between DLs. The phase 2 portion of the study is ongoing at DL2 as is expanded enrollment on a combination cohort of liso-cel plus ibrutinib.

KEY POINTS

- FCR as initial therapy for patients with mutated IGHV and non-17p13 deletion can result in very prolonged survival.
- Ibrutinib and acalabrutinib target BTK and are approved by the FDA for both initial treatment and for relapsed/refractory CLL.
- Idelalisib with rituximab and duvelisib are approved for treatment of relapsed/refractory CLL in less fit patients, but the substantial risks of colitis and serious infections limit use.
- Venetoclax is approved for both treatment-naïve and relapsed CLL and can cause tumor lysis syndrome in patients with high disease burden, which is why a gradual ramp-up of dosing is employed.
- Treatment of relapsed CLL generally is determined based on which class of agents was used initially. Although prospective studies are lacking, current data suggest that either sequence (BTKi then BCL2i or BCL2i then BTKi) is appropriate.
- Investigative therapies, including combination studies and CAR-T, have the potential to continue to improve standard of care in the next few years.

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Complications of CLL

The course of CLL is complicated by defective innate and acquired immune function that develops early in the clinical course of the disease. This immune dysfunction generally becomes more severe with disease progression and is exacerbated by conventional therapies. Immunodeficiency increases the risk of infection and autoimmune disease, and defective immune surveillance could contribute to the increase risk of second malignancy. CLL patients are also at increased risk of clonal evolution to aggressive lymphoma (Richter transformation).

Infections

Serious infections result in considerable morbidity and are a major cause of death in CLL patients. Defective responses to antigens by nonmalignant B cells result in quantitative and qualitative defects in antibody production. Although absolute T-cell counts are usually increased in patients with CLL, CD4/CD8 ratios are reversed with decreased T-cell receptor repertoire and markedly impaired T-cell function. Innate immunity is impaired by monocyte, dendritic, and natural killer (NK)-cell dysfunction; decreased serum complement levels; and bone marrow failure–associated neutropenia.

Clinical

Impaired humoral immunity markedly increases the risk of overwhelming bacterial infections by encapsulated organisms (eg, *Streptococcus pneumoniae* and *Staphylococcus aureus*) at all stages of CLL. Defective T-cell immunity increases the risk of herpesvirus reactivation. Reactivation of varicella-zoster virus results in shingles, which is frequently complicated by postherpetic neuralgia and can also lead to disseminated varicella-zoster. Herpes simplex virus reactivation can result in local lymphadenitis and systemic herpes simplex virus infections. CMV reactivation is more common in patients with advanced-stage disease and those treated with lymphotoxic therapies. CLL patients with advanced-stage disease and those undergoing immunosuppressive therapy or allogeneic hematopoietic stem cell transplantation are at high risk of fungal and atypical bacterial infections. Idelalisib is associated with significant infectious complications, as discussed previously. Ibrutinib has also been associated with early-onset fungal infection, especially in patients with other predisposing risk factors, including the use of corticosteroids.

Prevention

Preventive measures, education, and rapid and effective responses to infection can decrease the risk and consequences of serious infections. Patients need to be trained to recognize and to seek immediate medical examination for serious infections, especially when indicated by fevers. Vaccination responses are usually suboptimal in patients with CLL. However, pneumococcal vaccine responses can be improved by addition of the conjugated 13-valent vaccine to the standard 23-valent polysaccharide vaccine. Influenza vaccines are likely to be of most value in patients with early-stage CLL but should be, if possible, administered to all patients and household members. Live-virus vaccines (eg, yellow fever) are contraindicated.

Prophylactic antimicrobial therapy is not of proven value in CLL. *Pneumocystis* and herpesvirus prophylaxis is commonly used during and after therapies with lymphotoxic drugs (eg, purine analogs and high-dose corticosteroids). Prophylactic antiviral therapy can be useful in decreasing the risk of varicella-zoster virus and herpes simplex virus reactivation in patients with recurrent infections. In contrast to Zostavax, which carries a risk of viral infection because it is an attenuated virus vaccine, a recombinant varicella-zoster vaccine (Shingrix) is now available and is safe to use in patients with CLL.

The use of intravenous immunoglobulin (IVIG) in management of CLL is not well established. IVIG 0.4 mg/kg/4 wk has been shown to decrease the risk of infections but may not extend OS. IVIG can cause serious adverse events and is expensive. Its use should probably be limited to patients with recurrent major infections (at least 2 in 6 months) and should not be based on immunoglobulin (IgG) levels alone. Subcutaneous formulations are also available for home use.

Effective observation and treatment of infections in patients with CLL can be challenging. Infection evaluation should focus on encapsulated bacteria and atypical and opportunistic infections. Treatment should assume that all CLL patients are immune compromised. The NCCN Clinical Practice Guidelines for the Prevention and Treatment of Cancer-Related Infections provides comprehensive recommendations.

Autoimmune disease

Approximately 5% to 10% of CLL patients have autoimmune complications, most of which are hematologic (eg, autoimmune hemolytic anemia [AIHA] or immune thrombocytopenia).

Hematologic disease

Most (>90%) autoimmune cytopenia is caused by loss of self-tolerance that is attributed to disruption of T-cell function by CLL cells. This disruption causes pathological production of high-affinity polyclonal IgG antibodies

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directed against blood cell antigens by nonmalignant B cells, which results in autoimmune hemolytic anemia or immune thrombocytopenia purpura (ITP). In contrast, production of a self-reactive monoclonal antibody (usually IgM) by CLL cells is rare and occurs in <10% of patients with AIHA or ITP. Pure RBC aplasia (PRCA) can be mediated by either autoantibodies or direct T-cell cytotoxicity. Autoimmune cytopenias occur throughout the course of CLL and cause 15% to 20% of noniatrogenic cytopenias in CLL patients. Patients with autoimmune cytopenia should not be classified as having advanced-stage disease unless they have concomitant bone marrow failure demonstrated by bone marrow biopsy results.

AIHA

Clinical. AIHA is usually characterized by reticulocytosis in the absence of bleeding, elevated serum lactate dehydrogenase and indirect bilirubin levels, and positive findings of a direct antiglobulin test (DAT) that detects surface-bound anti-RBC IgG antibodies and the complement degradation product C3d. However, patients with AIHA- and CLL-related bone marrow failure (complex AIHA) are often not able to generate a reticulocyte response to anemia. Although DAT test results are positive in >90% of CLL patients with AIHA, ~15% to 20% of CLL patients have positive DAT results during the course of their disease and only 35% of these patients develop AIHA.

Management. Patients with AIHA and adequate erythropoiesis (simple AIHA) can be treated with immunosuppression using corticosteroids. Patients with severe anemia or a slow response to corticosteroid therapy can benefit from addition of IVIG. AIHA relapses are common, and many patients require long-term immunosuppression or additional treatment, such as anti-CD20 monoclonal antibodies. Patients with both AIHA- and CLL-related bone marrow failure require treatment of both conditions. Because purine analogs are myelosuppressive and can cause autoimmune cytopenia when used as monotherapy, these agents should probably be avoided. Therapy with ibrutinib has also been shown to be very effective in management of CLL-associated AIHA. Splenectomy is less effective here than in patients with idiopathic AIHA.

ITP

Clinical. CLL patients with progressive bone marrow failure usually develop anemia first and thrombocytopenia subsequently. CLL patients presenting with thrombocytopenia without anemia should be examined for causes of platelet sequestration. A bone marrow examination may be helpful in this scenario. In patients with insidious-onset thrombocytopenia and platelet counts of $>50 \times 10^9$/L, hypersplenism should be considered. In contrast, acute-onset (<2 weeks) or severe thrombocytopenia (platelet counts of $<30 \times 10^9$/L) in CLL patients is more likely to be caused by ITP. Antiplatelet antibody assays have low specificity and sensitivity, and they are not useful in making the diagnosis of ITP, which remains one of exclusion.

Management. Patients with no bleeding complications and platelet counts of $>20 \times 10^9$/L should be carefully observed and educated, but they do not need active treatment. Those needing treatment usually respond to immunosuppression with corticosteroids. Thrombopoietin agonists can be useful if patients have a slow or inadequate response to immunosuppression. Splenectomy is considered less effective in CLL patients compared to primary ITP. Patients with ITP and bone marrow failure can be treated with regimens similar to those used to manage complex AIHA. Caution is advised with use of ibrutinib in the presence of severe thrombocytopenia because of the increased risk of bleeding.

PRCA

Clinical. Autoimmune PRCA presents with anemia, a very low absolute reticulocyte count, and no evidence of hemolysis or bleeding. A definitive diagnosis requires a bone marrow study showing an erythroid-lineage maturation arrest. The differential diagnosis includes parvovirus and other virus infections. Because patients with CLL have inadequate humoral immune response to infections, detection of parvovirus and CMV viremia by polymerase chain reaction is more useful than viral serology.

Management. PRCA should be treated with immunosuppression using prednisone and cyclosporine. Clinical improvement is often slow because of the lag time to restoration of erythropoiesis. Long-term immunosuppression is frequently required to maintain adequate hemoglobin levels.

Autoimmune neutropenia

This is a rare and poorly understood condition that should be considered in patients with isolated neutropenia of uncertain etiology, especially if it is severe. A bone marrow examination should be considered to help in the differential diagnosis. Large granular lymphocyte-associated neutropenia should also be considered.

Nonhematologic disease

Patients with CLL have an increased risk of autoimmune-acquired angioedema, paraneoplastic pemphigus, and glomerulonephritis. A clinically important

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consequence of immune dysregulation in CLL patients is exaggerated cutaneous arthropod-bite reactions, which can be complicated by cellulitis and transient painful adenopathy and is often mistaken by patients for disease progression.

Second malignancies

Hematologic malignancies

Lymphoid malignancies

DLBCL can occur at any time in the course of CLL (Richter transformation, incidence ~0.5% per year) with the highest risk in patients with *NOTCH1* mutations and 17p13 deletion/*TP53* mutation. In ~80% of patients with CLL who develop a DLBCL, a CLL cell undergoes clonal transformation to a highly aggressive DLBCL with very poor prognosis. In contrast, ~20% of CLL patients developing DLBCL have clonally unrelated de novo DLBCL with a considerably more favorable prognosis. These 2 etiologies can be distinguished by VDJ rearrangement analysis of paired CLL and DLBCL cell samples. Diagnosing de novo DLBCL is challenging. Testing for clonality may not be readily available to the practitioner. Patients with CLL are also at increased risk of developing Hodgkin lymphoma and other B-cell malignancies.

Management. CLL patients diagnosed with de novo DLBCL require standard examination and treatment. There is no standard of care for clonally evolved DLBCL in patients with CLL. Clinical trials should always be considered for clonally evolved DLBCL because standard intensive therapy is usually not very effective. Allo-SCT should be attempted if the patient is eligible.

Nonhematologic malignancies

Skin cancer

CLL markedly increases the risk and aggressiveness of skin malignancies. Squamous cell carcinoma and basal-cell carcinoma are increased 5- to 10-fold and have more aggressive biology with increased risk of local invasion and distant metastasis. The risk of melanoma is significantly increased with more aggressive biology and poorer outcome.

Management. Patients need to be educated about limiting ultraviolet radiation exposure and undergoing frequent skin checks with prompt examination and care of suspicious lesions. Patients should be seen at least annually by a skilled dermatologist.

Other malignancies

CLL patients are at increased risk of noncutaneous second malignancies, which are a major cause of morbidity and mortality. Patients should minimize high-risk behavior and follow standard cancer-preventive screening guidelines.

KEY POINTS

- CLL is associated with both significant humoral and T-cell-mediated immunodeficiency, which leads to an increased risk of infection even for untreated CLL.
- Five to ten percent of CLL patients have autoimmune complications, the most common being AIHA and ITP.
- Transformation to diffuse large B-cell lymphoma and Hodgkin lymphoma are seen in increased frequency in CLL.
- CLL is associated with an increased incidence of both nonmelanoma and melanoma skin cancers that may be more clinically aggressive.

B-cell prolymphocytic leukemia

B-cell prolymphocytic leukemia is a very rare mature B-cell lymphoid malignancy with a median age at diagnosis of 69 years and equivalent incidence in males and females.

Clinical presentation

Patients with B-PLL usually present with very high ALC (>100,000), splenomegaly that can be massive, and minimal or no lymphadenopathy.

Diagnosis

Diagnosis is suggested by a high percentage (~90%) of lymphocytes with prolymphocytic morphology. These cells are medium sized with large, condensed nuclei, a prominent large nucleolus, and a small amount of basophilic cytoplasm without cytoplasmic projections. On flow cytometric analysis, these B-PLL cells are monoclonal B cells that have bright light-chain and CD20 expression, and they usually do not express CD5 or CD23. These features are useful in differentiating primary B-PLL from CLL with high levels of prolymphocytes and the leukemic phase of mantle cell lymphoma. The other considerations in the differential diagnosis are marginal zone lymphoma and hairy cell leukemia.

Genetic analysis

FISH analysis for t(11;14) should be done to exclude the diagnosis of mantle cell lymphoma. Approximately 50% of patients have 17p13 deletion/*TP53* mutation that is associated with poorer responses to chemotherapy regimens.

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Treatment

B-PLL is a rare disease with limited data from clinical trials and no standard-of-care therapy. Patients with this disease should be referred to specialized lymphoid malignancy programs for treatment. Patients without 17p13 deletion/*TP53* mutation can respond to CIT regimens similar to those used in the treatment of CLL. Patients with 17p13 deletion/*TP53* mutation can respond to a combination of anti-CD20 monoclonal antibodies and alemtuzumab. There is very little published data on the use of BCR-pathway inhibitors to treat B-PLL.

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